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(54) Title: PIPERIDYL–IMIDAZOLE DERIVATIVES, THEIR PREPARATIONS AND THERAPEUTIC USES

(57) Abstract

Piperidyl–imidazole derivatives pharmaceutical compositions comprising them and use thereof in the treatment and/or prevention of diseases and disorders related to the histamine H3 receptor. More particularly, the compounds are useful for the treatment and/or prevention of diseases and disorders, in which an interaction with the histamine H3 receptor is beneficial.

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PIPERIDYL-IMIDAZOLE DERIVATIVES, THEIR PREPARATIONS AND THERAPEUTIC USES

FIELD OF THE INVENTION

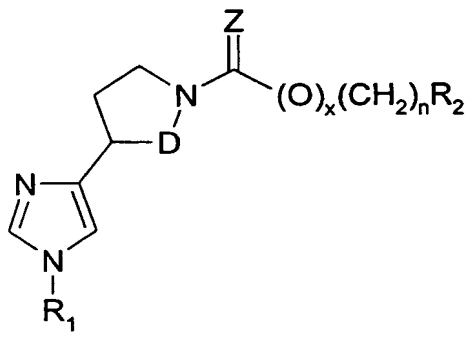
The present invention relates to novel substituted imidazoles, to methods for their preparation, to the use of these compounds as medicaments, to pharmaceutical compositions comprising the compounds, and to a method of treatment employing these compounds and compositions. The present compounds show a high and selective binding affinity to the histamine H3 receptor indicating histamine H3 receptor antagonistic or agonistic activity. As a result, the compounds are useful for the treatment and/or prevention of diseases and disorders related to the histamine H3 receptor.

BACKGROUND OF THE INVENTION

The existence of the histamine H3 receptor has been known for several years and the receptor is of current interest for the development of new medicaments (see eg Stark, H.; Schlicker, E.; Schunack, W., *Drugs Fut.* **1996**, *21*, 507-520; Leurs, R.; Timmerman, H.; Vollinga, R. C., *Progress in Drug Research* **1995**, *45*, 107-165). Recently, the human histamine H3 receptor has been cloned, cf Lovenberg, T.W. et al, *Molecular Pharmacology*, **June 1999**, *55*, 1101-1107. The histamine H3 receptor is a presynaptic autoreceptor located both in the central and the peripheral nervous system, the skin and in organs such as the lung, the intestine, probably the spleen and the gastrointestinal tract. The histamine H3 receptor has been demonstrated to regulate the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. A histamine H3 receptor antagonist would therefore be expected to increase the release of these neurotransmitters in the brain. A histamine H3 receptor agonist, on the contrary, leads to an inhibition of the biosynthesis of histamine and an inhibition of the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. These findings suggest that histamine H3 receptor agonists and antagonists could be important mediators of neuronal activity. Accordingly, the histamine H3 receptor is an important target for new therapeutics.

Several publications disclose the preparation and use of histamine H3 agonists and antagonists.

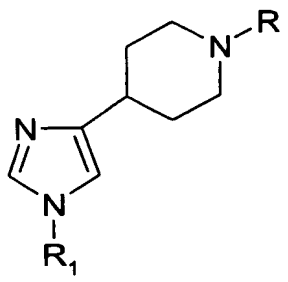
Thus, US patent No. 5,486,526 (corresponding to WO No. 95/11894) (the University of Toledo) discloses piperidyl-imidazole derivatives, which are stated to be potent histamine H3 receptor antagonists. More particularly, piperidyl-imidazole derivatives of the following formula are disclosed:



wherein R_1 i.a. represents hydrogen or an *in vivo* hydrolyzable group; D represents CH_2 or CH_2CH_2; Z represents O or S; x is 0 or 1; n is an integer from 0 to 6; and R_2 represents a substituted or unsubstituted linear chain or branched chain alkyl group of up to about 20 carbon atoms, a substituted or unsubstituted carbocyclic group of up to about 20 carbon atoms or a substituted or unsubstituted aryl group of up to about 20 carbon atoms.

The compounds according to the invention differ structurally from these known compounds by bearing a tertiary nitrogen atom in the side chain attached to the nitrogen atom of the piperidinyl group.

EP No. 0 494 010 (INSERM et al.) discloses piperidine derivatives of the following general formula which are stated to possess histamine H3 receptor antagonistic activity:



wherein R_1 i.a. represents a hydrogen atom; and R i.a. represents

i) a group COR_3 wherein R_3 i.a. represents

a linear chain or branched chain alkyl group of from 1 to 11 carbon atoms,

a group $-(CH_2)_nR_4$ wherein n is an integer from 1 to 10 and R_4 i.a. represents a non-aromatic carbocyclic ring system, a phenyl group optionally substituted or thionyl,

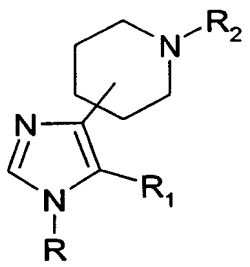
a group $-CH=CHR_8$ wherein R_8 represents a non-aromatic carbocyclic ring system, or

a secondary amine group $-NH(CH_2)_nR_9$ wherein n is an integer from 1 to 5 and R_9 represents a non-aromatic carbocyclic ring system or a phenyl group optionally substituted, or

ii) a group $-C(=S)NH(CH_2)_nR_9$ wherein n is an integer from 1 to 5 and R_9 represents a non-aromatic carbocyclic ring system or a phenyl group optionally substituted.

The present compounds differ from these known compounds by bearing a tertiary nitrogen atom in the side chain attached to the nitrogen atom of the piperidinyl group.

Furthermore, EP No. 0 197 840 (INSERM et al.) discloses piperidine derivaties of the following general formula which are stated to possess histamine H3 receptor antagonistic activity:



wherein R_1 is hydrogen, methyl or ethyl, R i.a. is hydrogen, and R_2 i.a. represents a linear chain or branched chain C_{1-6}-alkyl group, a 3-(1-benzimidazolonyl) propyl group or a group $-(CH_2)_n-X-(phenyl-R_3)$ wherein n is an integer from 0 to 3, X i.a. is -NH-, a bond or -CH=CH- and R_3 i.a. represents hydrogen, methyl, halogen or trifluoromethyl.

When R_2 represents 3-(1-benzimidazolonyl) propyl a tertiary nitrogen atom is present in the side chain of the piperidinyl group of the known compounds. In this case, however, the tertiary nitrogen atom is forming part of a specific ring system viz. the 1-benzimidazolonyl group, which is not embraced by the present invention. None of the remaining known compounds contains a tertiary nitrogen atom in the side chain attached to the nitrogen atom of the piperidinyl group. Accordingly, the know compounds differ from the present compounds.

In view of the art's interest in histamine H3 receptor agonists and antagonists, novel compounds which interact with the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a specific class of substituted imidazole compounds has a high and specific affinity to the histamine H3 receptor. Some of these substituted imidazole derivatives are novel per se thereby constituting a further aspect of the invention.

Due to their interaction with the histamine H3 receptor, the present compounds are useful in the treatment and/or prevention of a wide range of conditions and disorders in which an interaction with the histamine H3 receptor is beneficial. Thus, the compounds may find use eg in the treatment of diseases of the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

DEFINITIONS

In the structural formulas given herein and throughout the present specification, the following terms have the indicated meaning:

The term "C_{1-6}-alkyl" as used herein represents a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to the radical -O-C_{1-6}-alkyl where C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_{3-8}-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), phenanthrenyl, fluorenyl, indenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1-(1,2,3,4-tetrahydronaphthyl) and 2-(1,2,3,4-tetrahydronaphthyl).

The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl and the like. Heteroaryl is also intended to include the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially or fully hydrogenated derivatives are pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, diazepinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, oxazolinyl, oxazepinyl, aziridinyl and tetrahydofuranyl.

The term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein, the phrase "mono-, bi- or polycyclic ring system" is intended to include all the carbocyclic and heterocyclic ring systems that R^3 and R^4 according to their definitions are able to form with the linker group and the nitrogen atom to which they are attached. Non-limiting examples of such ring systems are systems containing one to five cycles, eg two to four cycles such as 5,11-dihydro-5*H*-dibenz-[*b,e*][1,4]oxazepin-5-yl, 5,11-dihydro-5*H*-dibenz[*b,e*][1,4]thiazepin-5-yl, 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl, phenothiazin-10-yl, phenoxazin-10-yl and 9H-tribenzo[*b,d,f*]azepin-9-yl which may optionally be substituted, eg with halogen or C_{1-6}-alkoxy.

Certain of the above defined terms may occur more than once in the structural formulas, and upon such occurrence each term shall be defined independently of the other.

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified.

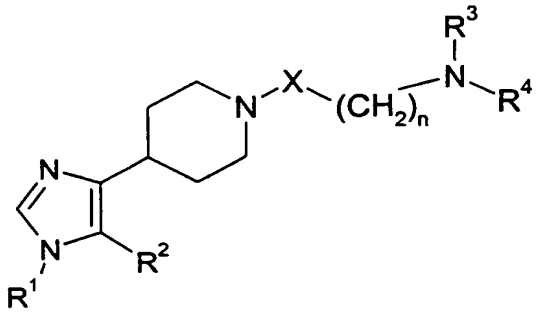
When the groups in question are substituted with more than one substituent the substituents may be the same or different.

As used herein, the phrase "a functional group which can be converted to hydrogen *in vivo*" is intended to include any group which upon administering the present compounds to the subjects in need thereof can be converted to hydrogen eg enzymatically or by the acidic environment in the stomach. Non-limiting examples of such groups are acyl, carbamoyl, monoalkylated carbamoyl, dialkylated carbamoyl, alkoxycarbonyl, alkoxyalkyl groups and the like such as C_{1-6}-alkanoyl, aroyl, C_{1-6}-alkylcarbamoyl, di-C_{1-6}-alkylcarbamoyl, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkoxy-C_{1-6}-alkyl.

As used herein, the phrase "diseases and disorders related to the histamine H3 receptor" is intended to include any disease or disorder in which an effect, either antagonistic or agonistic, on the histamine H3 receptor is beneficial.

DESCRIPTION OF THE INVENTION

The present invention relates to novel substituted imidazoles of the general formula I



(I)

wherein

R^1 is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, cyano, halogen or C_{1-6}-alkyl;

wherein C_{1-6}-alkyl is optionally substituted with cyano, halogen, amino, nitro, trifluoromethyl or C_{1-6}-alkoxy;

X is –C(=O)-, -C(=S)- or -CH_2-;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

R^3 and R^4 independently are

C_{3-8}-cycloalkyl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

aryl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

heteroaryl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl; or

C_{1-6}-alkyl optionally substituted with halogen, C_{1-6}-alkoxy, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

wherein C_{3-8}-cycloalkyl, aryl and heteroaryl optionally are substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino or cyano;

which groups R^3 and R^4 optionally may be connected by one or more bridging linkers to form, together with the nitrogen atom to which they are attached, a mono-, bi- or polycyclic ring system;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^3 and R^4 may optionally be connected by one or more bridging linkers independently selected from a bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-$, $-(CH_2)_{0-4}-S-(CH_2)_{0-4}-$, phenylene and biphenylene to form, together with the nitrogen atom to which they are attached, a mono-, bi- or polycyclic ring system.

In a preferred embodiment of the invention R^1 and R^2 are both hydrogen.

In another preferred embodiment of the invention X is –C(=O)- or $-CH_2-$.

In still another preferred embodiment of the invention n is 1 to 5, preferably 2, 3 or 4.

In yet another preferred embodiment of the invention R^3 and R^4 are both aryl, preferably phenyl optionally substituted as defined above for formula I.

Preferably, the phenyl groups are unsubstituted.

When the phenyl groups are substituted the substituents are preferably selected from halogen, C_{1-6}-alkoxy such as methoxy or ethoxy, C_{1-6}-alkyl such as methyl, ethyl, n-propyl, i-propyl, i-butyl or *tert*-butyl, trifluoromethyl, nitro, amino and cyano.

In a further preferred embodiment of the invention R^3 and R^4 are connected via one or more bridging linkers selected from a bond, C_{1-4}-alkylene such as ethylene or propylene, C_{2-4}-alkenylene such as ethenylene or propenylene, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-$ such as -O- or oxy-C_{1-4}-alkylene such as oxymethylene, oxyethylene or oxypropylene,
$-(CH_2)_{0-4}-S-(CH_2)_{0-4}-$ such as -S- or thio-C_{1-4}-alkylene such as thiomethylene, thioethylene or thiopropylene, phenylene and biphenylene to form, together with the nitrogen atom to which they are attached, a mono-, bi- or polycyclic ring system such as a mono-, bi-, tri- or tetracyclic system.

Preferably, R^3 and R^4 are connected via one linker.

Preferably, the linker is selected from C_{1-4}-alkylene such as ethylene or propylene, -S-, phenylene such as 1,2-phenylene and oxy-C_{1-4}-alkylene such as oxyethylene or oxypropylene. Preferred among these is C_{1-4}-alkylene such as ethylene or propylene, especially ethylene.

In still a preferred embodiment of the invention R^3 and R^4 are both representing phenyl groups which are connected via a C_{1-4}-alkylene linker, preferably ethylene. The phenyl groups may optionally be substituted as defined above for formula I but preferably they are unsubstituted.

When they are substituted the substituents are preferably selected from halogen, C_{1-6}-alkoxy such as methoxy or ethoxy, C_{1-6}-alkyl such as methyl, ethyl, n-propyl, i-propyl, i-butyl or *tert*-butyl, trifluoromethyl, nitro, amino and cyano.

Specific examples of the above-preferred embodiments of the present invention are the following compounds:

3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)propan-1-one;

5-(3-(4-(1*H*-Imidazol-4-yl)piperidin-1-yl)propyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine;

4-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one;

4-Diphenylamino-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one;

5-(4-(4-(1*H*-Imidazol-4-yl)piperidin-1-yl)butyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine;

1-(4-(1*H*-Imidazol-4-yl)piperidin-1-yl)-4-(phenothiazin-10-yl)butan-1-one;

4-(2-Bromo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one;

4-(9H-Tribenzo[*b,d,f*]azepin-9-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one; and

4-(5,11-Dihydro-5*H*-dibenzo[*b,e*][1,4]oxazepin-5-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic,

malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan. Such solvates are also contemplated as being within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into the present compounds. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The compounds of the present invention interact with the histamine H3 receptor and may thus be used for the treatment of a wide range of conditions and disorders in which histamine H3 receptor interactions are beneficial.

Accordingly, in another aspect the present invention relates to a compound of the general formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of a compound of the general formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and/or prevention of disorders or diseases related to the histamine H3 receptor.

In still another aspect, the invention relates to a method for the treatment and/or prevention of disorders or diseases related to the histamine H3 receptor the method comprising administering to a subject in need thereof an effective amount of a compound of the formula I as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same.

More particularly, the present compounds may possess histamine H3 receptor antagonistic activity and would accordingly be useful in the treatment of a wide range of conditions and disorders in which a histamine H3 receptor blockade is beneficial.

In a preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the reduction of weight.

In a preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of overweight or obesity.

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the suppression of appetite or satiety induction.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity such as atherosclerosis, hypertension, IGT (impaired glucose tolerance), diabetes, especially Type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers.

In yet a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

The compounds of the present invention may also be used for the treatment of air-way disorders such as asthma, as anti-diarrhoeals and for the modulation of gastric acid secretion.

Furthermore, the compounds of the present invention may be used for the treatment of diseases associated with the regulation of sleep and wakefulness and for the treatment of narcolepsy and attention deficit disorders.

Moreover, the compounds of the invention may be used as stimulants or as sedatives.

The present compounds may also be used for the treatment of conditions associated with epilepsy. Additionally, the present compounds may be used for the treatment of motion sickness and vertigo. Furthermore, they may be useful as regulators of hypothalamo-hypophyseal secretion, antidepressants, modulators of cerebral circulation, and in the treatment of irritable bowel syndrome.

Further, the compounds of the present invention may be used for the treatment of dementia and Alzheimer's disease.

The present novel compounds may also interact with the vanilloid receptors, the serotonin receptors, and the adrenergic receptors and may be useful for the treatment of diseases associated with these receptors. Hence, the compounds of the present

invention may be vanilloid receptor agonists, and thus be useful for the treatment of obesity by enhancement of the metabolic rate and energy expenditure. Further, by virtue of their interaction with the vanilloid receptor the compounds of the present invention may be useful for the treatment of pain or neurogenic inflammation or inflammatory painful conditions.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the vanilloid receptor such as for the treatment and/or prevention of pain, neurogenic inflammation or obesity.

Furthermore, the present compounds may interact with the 5-HT3 receptor (serotonin-3-receptor) and may accordingly be useful as antiemetics, in particular the chemotherapy-induced emesis. Further potential applications of 5-HT3 antagonists include treatment of central nervous system disorders such as anxiety, schizophrenia, drug abuse and withdrawal symptoms, and pathological and age-associated amnesia.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the serotonin-3 receptor (5-HT3) such as for the treatment of emesis.

Furthermore, the present compounds may interact with the adrenergic alpha-2 receptor and thus be useful for the treatment of hypertension and of conditions associated with overexpression or hypersensitization of the adrenergic alpha-2 receptor, especially obesity, withdrawal symptoms to an adrenergic alpha-2 agonist, neurological disorders (especially orthostatic hypotension), multiple system atrophy, diabetes mellitus, benign prostatic hyperplasia or drug induced sensitization of the adrenergic alpha-2 receptor. Moreover, the compounds of the present invention, by virtue of their interaction with the alpha-2 receptor, may be useful as sedatives and hypnotics (sleep inducing agents) or as stimulants.

In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the alpha-2 adrenergic receptor such as for use as a sleep inducing agent.

The present compounds may be administered in combination with one or more further pharmacologically active substances eg selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sensitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR and RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells.

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 to Dr. Reddy's Research Foundation.

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 to Dr. Reddy's Research Foundation.

In a further embodiment the present compounds are administered in combination with an α-glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and met-

formin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to *Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA,* **1995**.

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharma-ceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in *Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA,* **1995**.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred

route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration

one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound according to the invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound according to the invention with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material

known in the art such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds according to the invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet, which may be prepared by conventional tabletting techniques, may contain:

Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Lactosum Ph. Eur.	67.8 mg
Cellulose, microcryst. (Avicel)	31.4 mg
Amberlite	1.0 mg
Magnesii stearas Ph. Eur.	0.25 mg

Coating:

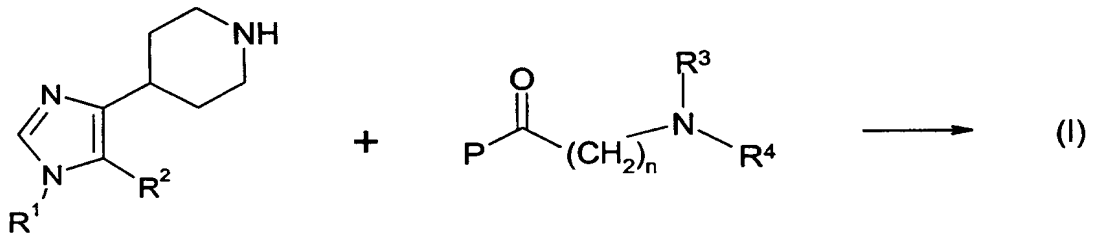
HPMC approx.	9 mg
Mywacett 9-40 T* approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula I in combination with one or more other pharmacologically active substances.

The preparation of the compounds according to the invention can be realized in many ways.

The compounds of formula I wherein X is -C(=O)- and n, R^1, R^2, R^3 and R^4 are as defined for formula I may be prepared by the following method A:



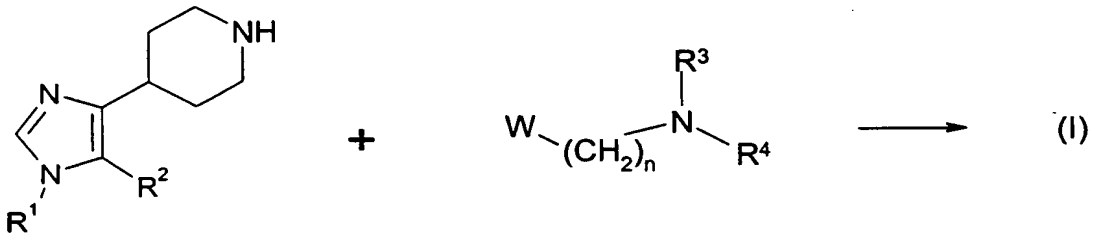
(II) (III) (I)

A compound of formula II wherein R^1 and R^2 are as defined for formula I may be reacted with a compound of formula III wherein R^3, R^4 and n are as defined for formula I and P is a suitable group providing an activated carboxylic acid derivative such as an acid chloride, an acid fluoride, an acid imidazolide, a *N*-hydroxybenzotriazolyl ester, an optionally substituted phenyl ester or it may be a symmetric anhydride, to give a compound of formula I wherein X is -C(=O)-. This acylation reaction may be carried out in a solvent such as dichloromethane, *N,N*-dimethylformamide, acetonitrile or *N*-methyl-2-pyrrolidone at a temperature

up to reflux temperature for the solvent used for eg 1 - 200 h. The reaction may be carried out in the presence of a base.

Compounds of formulas II and III are either commercially available or may readily be prepared by methods familiar to those skilled in the art.

Alternatively, the compounds of formula I wherein X is CH_2 and n, R^1, R^2, R^3 and R^4 are as defined for formula I may be prepared by the following method B:



(II) (IV)

A compound of formula II wherein R^1 and R^2 are as defined for formula I may be reacted with a compound of formula IV wherein R^3, R^4 and n are as defined for formula I and W is a suitable leaving group such as halogen, *p*-toluenesulfonate or mesylate to give a compound of formula I. This alkylation reaction may be carried out in a solvent such as acetonitrile, acetone, *N,N*-dimethylformamide, dibutyl ether, 2-butanone, ethyl acetate, tetrahydrofuran or toluene in the presence of a base eg potassium carbonate, sodium hydride and a catalyst, eg an alkali metal iodide at a temperature up to reflux temperature for the solvent used for eg 1 - 200 h.

Compounds of formulas II and IV are either commercially available or may readily be prepared by methods familiar to those skilled in the art.

EXAMPLES

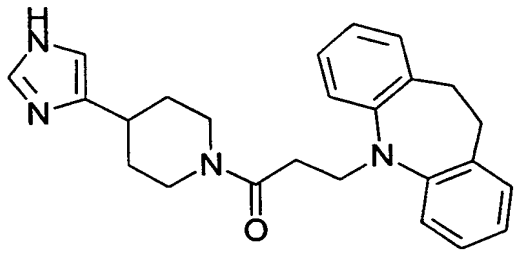
In the examples the following terms are intended to have the following, general meanings:

DMSO: dimethylsulfoxide
THF: tetrahydrofuran
m.p.: melting point

NMR spectra were recorded on Bruker 300 MHz and 400 MHz instruments. HPLC-MS was performed on a Perkin Elmer instrument (API 100), and HPLC-systems from Merck-Hitachi (Hibar™ RT 250-4, Lichrosorb™ RP 18, 5.0 µm, 4.0 x 250 mm, gradient elution, 20 % to 80 % acetonitrile in water within 30 min, 1.0 ml/min, detection at 254 nm) and Waters (Symmetry™, C_{18}, 3.5 µm, 3.0 x 150 mm, gradient elution, 5 % to 90 % acetonitrile in water within 15 min, 1.0 ml/min, detection at 214 nm) were used.

EXAMPLE 1

3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)propan-1-one



Following method A 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (50.0 g, 0.3 mol) was dissolved in *N,N*-dimethylformamide (700 ml). Under a nitrogen atmosphere, sodium hydride (12.3 g, 0.31 mol, 60 % dispersion in oil) was added in portions and the resulting mixture was stirred at 50 °C for 2 h. 3-Bromopropionic acid ethyl ester (65 ml, 0.51 mol) was added over 1.5 h and the mixture was stirred for 15 minutes before an additional amount of 3-bromopropionic acid ethyl ester (33 ml, 0.26 mol) was added

over 15 minutes. The reaction mixture was heated at reflux temperature overnight. After cooling, the mixture was evaporated *in vacuo*, and the residue was suspended in dichloromethane (150 ml). The solid was filtered off and the filtrate was evaporated *in vacuo*. The residue was purified in portions by column chromatography on silica gel using dichloromethane as eluent, affording 5.1 g (7 %) of 3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propionic acid ethyl ester as an oil.

TLC: R_f = 0.54 (SiO_2: dichloromethane).

The above ester (1.01 g, 3.42 mmol) was dissolved in ethanol (25 ml) and sodium hydroxide (0.71 g, 18 mmol) dissolved in water (5 ml) was added. The mixture was stirred at room temperature for 2 h. The mixture was acidified to pH ~3 using 1 M hydrochloric acid, and extracted with dichloromethane (2 x 35 ml). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propionic acid in quantitative yield.

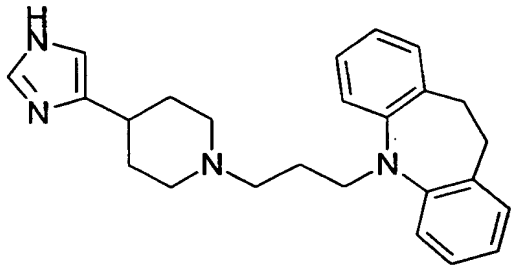
4-(4-Piperidyl)imidazole dihydrochloride (0.49 g, 2.2 mmol) was dissolved in methanol (5 ml) and sodium methoxide in methanol (0.8 ml, 30 %) was added. The mixture was stirred under nitrogen at room temperature for 1.5 h. At the same time, carbonyl diimidazol (0.33 g, 2.1 mmol) was dissolved in dichloromethane (4 ml), the above carboxylic acid (0.55 g, 2.1 mmol) was dissolved in dichloromethane (4 ml) and added, and the resulting mixture was stirred under nitrogen at room temperature for 1.5 h. The methanol solution was evaporated *in vacuo* and stripped with dichloromethane and the activated carboxylic acid mixture was added to the residue. The reaction mixture was stirred overnight at room temperature. Water (10 ml) and dichloromethane (50 ml) were added and the phases were separated. The dichloromethane phase was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (120 ml) using a mixture of methanol and ethyl acetate (1:5) as eluent to give 0.41 g (50 %) of the title compound as an amorphous product.

TLC: R_f = 0.28 (SiO_2: methanol/ethyl actetate = 1:5).

Calculated for $C_{25}H_{28}N_4O$, H_2O:
C, 71.75 %; H, 7.22 %; N, 13.38 %; Found:
C, 71.49 %; H, 7.13 %; N, 13.59 %.

EXAMPLE 2

5-(3-(4-(1*H*-Imidazol-4-yl)piperidin-1-yl)propyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine



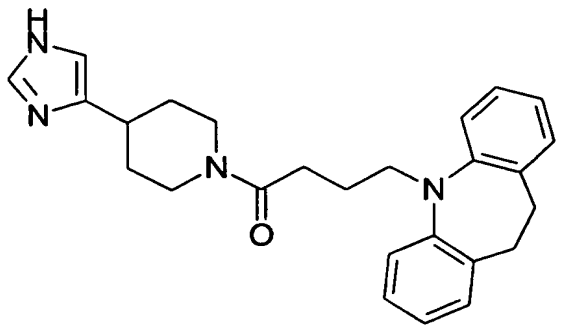
Following method B 4-(4-piperidyl)imidazole dihydrochloride (0.25 g, 1.1 mmol), 5-(3-chloropropyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (0.3 g, 1.1 mmol), potassium carbonate (0.46 g, 3.3 mmol) and potassium iodide (0.37 g, 2.2 mmol) were mixed in acetonitrile (10 ml) and the mixture was heated at reflux temperature for 20 h. After cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (125 ml) using a mixture of ethyl acetate and methanol (4:1) as eluent, affording 0.13 g (31 %) of the title compound.

TLC: R_f = 0.15 (SiO_2: ethyl acetate/methanol = 4:1).

Calculated for $C_{25}H_{30}N_4$, 1.25 H_2O, 0.2 $C_4H_8O_2$:
C, 72.64 %; H, 8.06 %; N, 13.13 %; Found:
C, 72.68 %; H, 7.93 %; N, 12.81 %.

EXAMPLE 3

4-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one



Following method A 5-(3-chloropropyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (2.5 g, 9.2 mmol) was dissolved in *N,N*-dimethylformamide (50 ml) and cooled on an ice-bath. Potassium cyanide (1.2 g, 18.4 mmol) was added in portions over 15 minutes and the reaction mixture was stirred on an icebath for 1 h and subsequently at room temperature for 6 days. Water was added (70 ml) and the mixture was extracted with toluene (100 ml). The toluene extract was dried ($MgSO_4$), evaporated *in vacuo* and stripped with dichloromethane. The residue was purified by column chromatography on silica gel (150 ml) using a mixture of dichloromethane and heptane (4:1) as eluent to give 1.81 g (75 %) of 4-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)butyronitrile as an oil.

TLC: R_f = 0.53 (SiO_2: dichloromethane).

The above nitrile (0.6 g, 2.3 mmol) was suspended in ethanol (6 ml). Potassium hydroxide (0.75 g, 13.4 mmol) was dissolved in water (2.5 ml) and added. The mixture was heated at reflux temperature overnight. After cooling, water (10 ml) was added and the solution was washed with toluene (15 ml). The aqueous solution was acidified with ~ 15 % hydrochloric acid (3 ml) and extracted with dichloromethane. The organic phase was evaporated *in vacuo* to give 0.63 g (97 %) of 4-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)butyric acid as an oil, which solidified on standing.

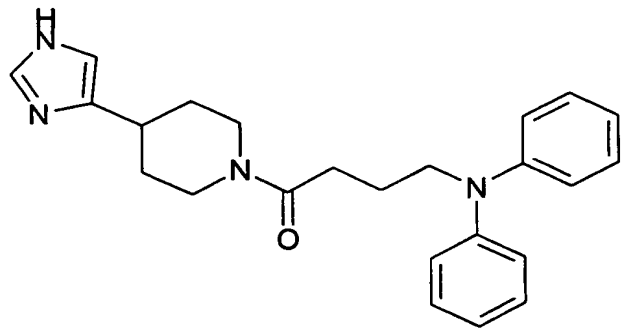
4-(4-Piperidyl)imidazole dihydrochloride (0.25 g, 1.1 mmol) was dissolved in methanol (4 ml) and 30 % sodium methoxide in methanol (0.42 ml, 2.3 mmol) was added. The mixture was stirred under nitrogen at room temperature for 1.5 h. At the same time, carbonyl diimidazol (0.17 g, 1.1 mmol) was dissolved in dichloromethane (5 ml), the above carboxylic acid (0.30 g, 1.11 mmol) was added and the resulting mixture was stirred under nitrogen at room temperature for 1.5 h. The methanol solution was evaporated *in vacuo* and stripped with dichloromethane (8 ml) and the activated carboxylic acid mixture was added to the residue. The reaction mixture was stirred overnight at room temperature. Water (10 ml) was added and the mixture was extracted with dichloromethane. The dichloromethane extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (50 ml) using a mixture of methanol and ethyl acetate (1:4) as eluent to give 0.28 g (60 %) of the title compound as an amorphous product.

TLC: R_f = 0.35 (SiO_2: methanol/ethyl acetate = 1:4).

Calculated for $C_{26}H_{30}N_4O$, 0.75 H_2O:
C, 72.95 %; H, 7.42 %; N, 13.09 %; Found:
C, 72.68 %; H, 7.46 %; N, 12.85 %.

EXAMPLE 4

4-Diphenylamino-1-(4-(1*H*-imidazol-4-yl)piperidin-1-yl)butan-1-one



Following method A diphenylamine (7.6 g, 45 mmol) was dissolved in dry diglyme (30 ml). Under a nitrogen atmosphere, sodium hydride (2.0 g, 50 mmol, 60 % dispersion in oil) was added in portions and the resulting mixture was stirred at 120 °C for 1 h. The mixture was cooled to 40 °C and 3-bromo-1-propyl tetrahydro-2-pyranyl ether (11.2 g, 50 mmol) was added and the reaction was heated to 130 °C over 30 minutes and then stirred at this temperature for 2 h. The reaction mixture was cooled to room temperature, poured into water (300 ml) and extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was dissolved in 2-propanol (150 ml) and 4 N sulfuric acid (25 ml) was added. The mixture was stirred at 60 °C for 30 minutes, half of the solvent was evaporated *in vacuo* and the mixture was diluted with water (300 ml) and neutralised with 4 N sodium hydroxide. The mixture was extracted with ethyl acetate (2 x 200 ml), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by chromatography on silica gel (150 g) using a mixture of heptane and tetrahydrofuran (8:2) to give 4.7 g (46 %) of 3-diphenylamino-1-propanol as an oil.

The above alcohol (3.8 g, 16.7 mmol) was dissolved in dry tetrahydrofuran (50 ml), triethylamine (2.5 ml, 18.4 mmol) was added and the reaction mixture was stirred at room temperature, while methanesulfonylchloride (1.9 g, 16.7 mmol) was added

dropwise. The reaction mixture was stirred for 2 h, the mixture was filtered and the solvent was evaporated *in vacuo*. The residue was dissolved in dry dimethylsulfoxide (25 ml) and potassium cyanide (2.2 g, 33 mmol) was added. The reaction mixture was heated to 85 °C and an additional amount of dry dimethylsulfoxide (25 ml) was added. Stirring was continued at 85 °C for 3 h. The reaction mixture was cooled and poured into cold water (500 ml) and extracted with ethyl acetate (2 x 200 ml). The combined organic phases were washed with water (100 ml), brine (100 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give 4.0 g of an oil, which was purified by column chromatography on silica gel (150 g) using a mixture of heptane and ethyl acetate (8:2) as eluent. This afforded 3.1 g (79 %) of 4-diphenylaminobutyronitrile.

The above butyronitrile (3.1 g, 13 mmol) was mixed with 96 % ethanol (40 ml) and potassium hydroxide (2.0 g). The mixture was heated at reflux temperature overnight. The solvent was evaporated *in vacuo*, and the residue was dissolved in water (200 ml) and washed with diethyl ether (2 x 25 ml). The solution was acidified with 1 N hydrochloric acid and the oily precipitate was extracted with ethyl acetate (2 x 100 ml), dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give 1.9 g (58 %) of 4-diphenylaminobutyric acid.

4-(4-Piperidyl)imidazole dihydrochloride (1.8 g, 8.0 mmol), was stirred in dry dichloromethane (10 ml) under an atmosphere of nitrogen, *N,N*-diisopropyl-*N*-ethylamine (2.8 ml, 16.0 mmol) was added and the mixture was stirred room temperature for 30 minutes. The above butyric acid (1.02 g, 4.0 mmol) was dissolved in dry dichloromethane (6 ml) under an atmosphere of nitrogen. 1-Hydroxy-7-azabenzotriazole (0.54 g, 4.0 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0,77g, 4.0 mmol) were added. The mixture was stirred for 15 minutes and then this activated reaction mixture was added to the reaction mixture first prepared. The combined reaction mixtures were stirred overnight at room temperature, diluted with dichloromethane (25 ml) and washed with water (2 x 20 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give an oil, which was purified by column chromatography on silicagel (100 g) using a mixture of

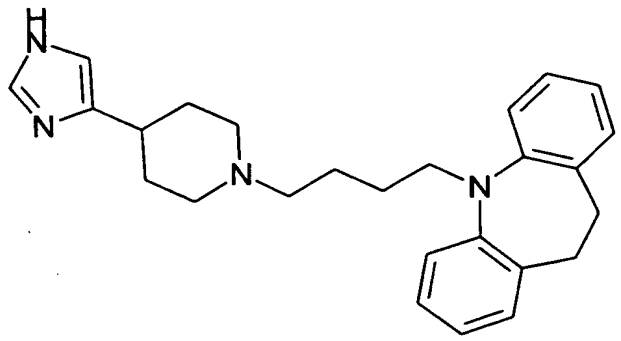
ethyl acetate and methanol (8:2) as eluent. This afforded 0.95 g (61 %) of the title compound.

TLC: R_f = 0.52 (SiO_2: ethyl acetate/methanol = 8:2).

^{1}H NMR (DMSO-d_6, 400 MHz): 1.28-1.48 (m, 2H) 1.78 (t, 2H) 1.87 (d, 2H) 2.37 (m, 2H) 2.60-2.79 (m, 2H) 3.05 (t, 1H) 3.71 (t, 2H) 3.84 (d, 1H) 4.40 (d, 1H) 6.67-6.79 (bs, 1H) 6.90 (t, 2H) 7.00 (d, 4H) 7.25 (t, 4H) 7.50 (s, 1H) 11.6-11.9 (bs, 1H).

EXAMPLE 5

5-(4-(4-(1*H*-Imidazol-4-yl)-piperidin-1-yl)butyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine



Following method B 4-(4-piperidyl)imidazole dihydrochloride (0.12 g, 0.53 mmol), 5-(4-chloro-1-butyl)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (0.15 g, 0.53 mmol), potassium carbonate (0.22 g, 1.6 mmol) and potassium iodide (0.18 g, 1.1 mmol) were mixed in acetonitrile and the mixture was heated at reflux temperature for 48 h. After cooling, water (10 ml) was added followed by ethyl acetate (10 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (10 ml), the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10 ml) using a mixture of ethyl acetate and methanol (4:1) as eluent, affording 0.94 g (20 %) of the title compound.

TLC: R_f = 0.05 (SiO_2: ethyl acetate/methanol = 4:1).

LCMS: 401.4 (MH^+).

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with the histamine H3 receptor was determined by the following *in vitro* binding assays.

Binding assay I

Rat cerebral cortex was homogenized in ice cold K-Hepes, 5 mM $MgCl_2$ pH 7.1 buffer. After two differential centrifugations the last pellet was resuspended in fresh Hepes buffer containing 1 mg/ml bacitracin. Aliquots of the membrane suspension (400 mg/ml) were incubated for 60 min at 25 °C with 30 pM [^{125}I]-iodoproxifan, a known histamine H3 receptor antagonist, and the test compound at various concentrations. The incubation was stopped by dilution with ice-cold medium, followed by rapid filtration through Whatman GF/B filters pretreated for 1 h with 0.5 % polyethyleneimine. The radioactivity retained on the filters was counted using a Cobra II auto gamma counter. The radioactivity of the filters was indirectly proportional to the binding affinity of the tested compound. The results were analyzed by nonlinear regression analysis.

Binding assay II

The H3-receptor agonist ligand R-α-methyl[^{3}H]histamine was incubated with isolated rat cortex cell-membranes at 25 °C for 1 h, followed by a filtration of the incubate through Whatman GF/B filters. Radioactivity retained on the filters was measured using a beta counter.

Male Wistar rats (150-200 g) were decapitated and cerebral cortex was quickly dissected out and frozen immediately on dry ice. Tissue was kept at –80 °C until membrane preparation. During the membrane preparation the tissue was kept on ice all the time. Rat cerebral cortex was homogenized in 10 volumes (w/w) ice-cold Hepes buffer (20 mM Hepes, 5 mM $MgCl_2$ pH 7.1 (KOH) + 1 mg/ml bacitracin) using an Ul-

tra-Turrax homogenizer for 30 seconds. The homogenate was centrifuged at 140 g in 10 min. The supernatant was transferred to a new test tube and centrifuged for 30 min at 23 000 g. Pellet was resuspended in 5-10 ml Hepes buffer, homogenized and centrifuged for 10 min at 23 000 g. This short centrifugation step is repeated twice. After the last centrifugation the pellet was resuspended in 2-4 ml Hepes buffer and the protein concentration was determined. The membranes were diluted to a protein concentration of 5 mg/ml using Hepes buffer, aliquoted and stored at –80 °C until use

50 µl test compound, 100 µl membrane (200 µg/ml), 300 µl. Hepes buffer and 50 µl R-α-methyl[^{3}H]histamine (1 nM) were mixed in a test tube. The compounds to be tested were dissolved in DMSO and further diluted in H_2O to the desired concentrations. Radioligand and membranes were diluted in Hepes buffer + 1 mg/ml bacitracin. The mixture was incubated for 60 min at 25 °C. Incubation was terminated by adding 5 ml ice-cold 0.9 % NaCl, followed by rapid filtration through Whatman GF/B filters pre-treated for 1 h with 0.5 % polyethyleneimine. The filters were washed with 2 x 5 ml ice-cold NaCl. To each filter a 3 ml scintillation cocktail was added and the radioactivity retained was measured with a Packard Tri-Carb beta counter.

IC_{50} values were calculated by non-linear regression analysis of binding curves (6 points minimum) using the windows program GraphPad Prism, GraphPad software, USA.

When tested, the present compounds of the formula I generally showed a high binding affinity to the histamine H3 receptor.

Preferably, the compounds according to the invention have an IC_{50} value as determined by one or both of the assays of less than 1 µM, more preferred of less than 500 nM and even more preferred of less than 100 nM.

The ability of the present compounds to reduce weight was determined using the *in vivo* open cage Schedule-fed rat model.

The open cage Schedule-fed rat model

Sprague-Dawley (SD) male rats of an age of about 1½ to 2 months and a weight of about 250 g were habituated to the presence of food (Altromin pelleted rat chow) in their home cage only during three hours in the morning from 9 to12 a.m. all days a week. Water was present ad libitum. When the consumption of food had stabilised after 7 to 9 days, the animals were ready for use.

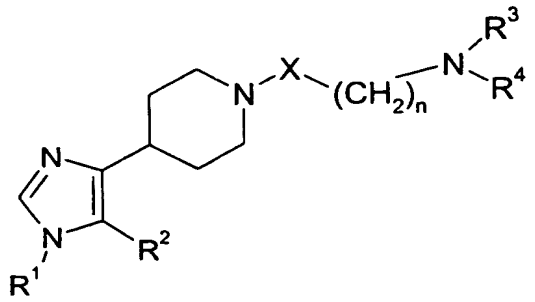
The animals were tested twice a week. During the test sessions, the test compound was administered intraperitoneally 30 minutes before the start of the sessions. One group of 9 animals were administered the test compound at a dose of 15 mg/kg and another group of 11 animals were administered the test compound at a dose of 30 mg/kg. A control group of 11 animals was administered the vehicle consisting of NaCl 0.9 % and Chremophor 5 %. Food and water intake were monitored at 1, 2 and 3 h post administration.

During the test period the animals were weighed weekly and if necessary extra food was given in order to ensure that the weight gain was 3 to 5 g per week corresponding to the normal weight gain for SD male rats at this age.

Any side effects were rapidly be discovered (barrel-rolling, bushy fur etc.) since the animals were kept in transparent plastic cages to enable continuous monitoring.

CLAIMS

1. A compound of the general formula I



(I)

wherein

R^1 is hydrogen or a functional group, which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, cyano, halogen or C_{1-6}-alkyl;

wherein C_{1-6}-alkyl is optionally substituted with cyano, halogen, amino, nitro, trifluoromethyl or C_{1-6}-alkoxy;

X is -C(=O)-, -C(=S)- or $-CH_2-$;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

R^3 and R^4 independently are

C_{3-8}-cycloalkyl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

aryl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

heteroaryl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl; or

C_{1-6}-alkyl optionally substituted with halogen, C_{1-6}-alkoxy, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl;

wherein C_{3-8}-cycloalkyl, aryl and heteroaryl optionally are substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino or cyano;

which groups R^3 and R^4 optionally may be connected by one or more bridging linkers to form, together with the nitrogen atom to which they are attached, a mono-, bi- or polycyclic ring system;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^3 and R^4 optionally may be connected by one or more bridging linkers independently selected from a bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-$, $-(CH_2)_{0-4}-S-(CH_2)_{0-4}-$, phenylene and biphenylene to form, together with the nitrogen atom to which they are attached, a mono-, bi- or polycyclic ring system.

3. A compound according to any one of the preceding claims wherein R^1 and R^2 are both hydrogen.

4. A compound according to any one of the preceding claims wherein X is -C(=O)- or $-CH_2-$.

5. A compound according to any one of the preceding claims wherein n is 2, 3 or 4.

6. A compound according to any one of the preceding claims wherein R^3 and R^4 are both aryl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl.

7. A compound according to claim 6 wherein R^3 and R^4 are both phenyl optionally substituted with halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, trifluoromethyl, nitro, amino, cyano, C_{3-8}-cycloalkyl, aryl or heteroaryl.

8. A compound according to claim 7 wherein R^3 and R^4 are both phenyl.

9. A compound according to any one of the preceding claims wherein R^3 and R^4 are connected by one or more bridging linkers selected from a bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-$, $-(CH_2)_{0-4}-S-(CH_2)_{0-4}-$, phenylene and bi-phenylene to form, together with the nitrogen atom to which they are attached, a mono-, bi-, tri- or tetracyclic system.

10. A compound according to claim 9 wherein R^3 and R^4 are connected by one bridging linker to form, together with the nitrogen atom to which they are attached, a tricyclic or tetracyclic system.

11. A compound according to claim 10 wherein the linker is -S-, phenylene, oxy-C_{1-4}-alkylene such as oxyethylene or oxypropylene or C_{1-4}-alkylene such as ethylene or propylene, preferably ethylene.

12. A compound according to claim 11 wherein the linker is ethylene.

13. A compound according to any one of the claims 1 to 12 for use as a medicament.

14. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 12 together with one or more pharmaceutically acceptable carriers or diluents.

15. A pharmaceutical composition according to claim 14 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 12.

16. Use of a compound according to any one of the claims 1 to 12 for the preparation of a medicament for the treatment and/or prevention of disorders and diseases related to the histamine H3 receptor.

17. Use of a compound according to any one of the claims 1 to 12 for the preparation of a medicament for the treatment and/or prevention of disorders and diseases, in which an inhibition of the histamine H3 receptor has a beneficial effect.

18. Use of a compound according to any one of the claims 1 to 12 for the preparation of a medicament having H3 antagonistic action.

19. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the reduction of weight.

20. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of overweight or obesity.

21. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the suppression of appetite or satiety induction.

22. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity.

23. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

24. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

25. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

26. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

27. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

28. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the serotonin-3 receptor (5-HT3) such as for use in the treatment of emesis.

29. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the vanilloid receptor such as for use in the treatment of pain, neurogenic inflammation or obesity.

30. Use of a compound according to any one of the claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders related to the alpha-2 adrenergic receptor such as for use as a sleep inducing agent.

31. A method for the treatment and/or prevention of disorders or diseases related to the H3 histamine receptor the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 12 or a pharmaceutical composition comprising the same.

32. The method according to claim 31, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00186

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, A61K 31/445, A61P 3/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0197840 A1 (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)), 15 October 1986 (15.10.86) --	1-32
A	WO 9320061 A1 (THE UNIVERSITY OF TOLEDO), 14 October 1993 (14.10.93) --	1-32
A	WO 9511894 A1 (THE UNIVERSITY OF TOLEDO ET AL), 4 May 1995 (04.05.95) -- --------	1-32

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2000	14 -08- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00186

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-32
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31-32 relate to method for treatment of the human or animal body a search has been carried out. The search have been based on the alleged effects of the claimed composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 00/00186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0197840 A1	15/10/86	ES 553351 A	16/03/87
		FR 2579596 A,B	03/10/86
		JP 2033924 C	19/03/96
		JP 7068239 B	26/07/95
		JP 61267574 A	27/11/86
		US 4707487 A	17/11/87
WO 9320061 A1	14/10/93	AU 3944593 A	08/11/93
		BR 9306190 A	23/06/98
		EP 0633882 A	18/01/95
		FI 944605 A	30/11/94
		HU 71353 A	28/11/95
		HU 9402827 D	00/00/00
		JP 7509219 T	12/10/95
		NO 943687 A	21/11/94
		SK 118794 A	07/06/95
		US 5486526 A	23/01/96
		US 5633382 A	27/05/97
		US 5639775 A	17/06/97
WO 9511894 A1	04/05/95	AU 7981594 A	22/05/95
		IL 111379 D	00/00/00
		US 5486526 A	23/01/96